Use of Chiral 1,3-Oxazolidine-2-thiones in the Diastereoselective Synthesis of Aldols

Yoshimitsu Nagao,*[a] Shozo Yamada,[a] Toshio Kumagai,[a] Masahito Ochiai,[a] and Eiichi Fujita*[b]

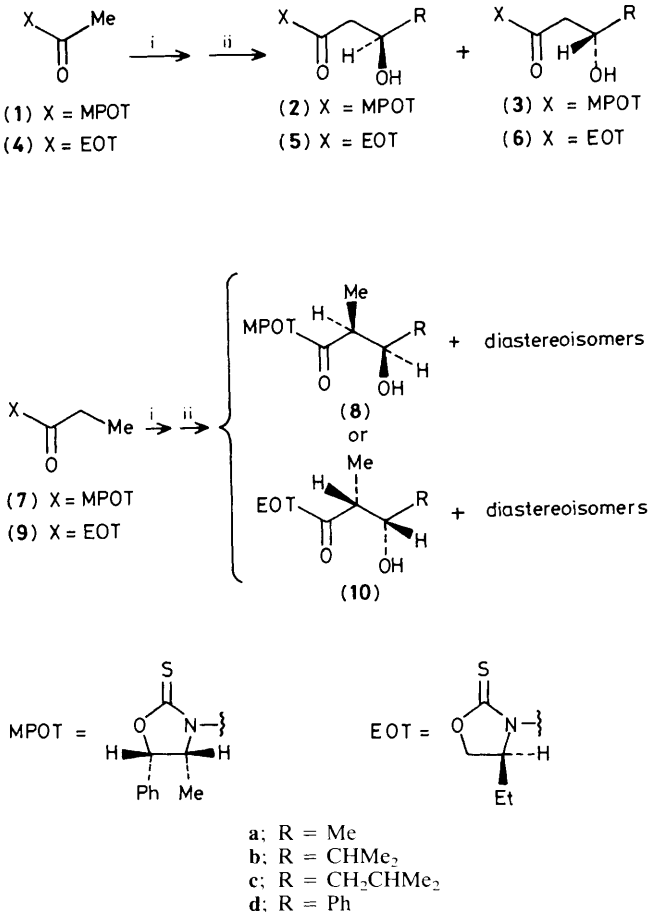
[a] *Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan*
[b] *Osaka College of Pharmacy, 10–65 Kawai 2-Chome, Matsubara 580, Japan*

A useful diastereoselective synthesis of aldols using chiral 3-acyl-1,3-oxazolidine-2-thiones, (**1**), (**4**), (**7**), and (**9**), is reported and its application to the synthesis of a chiral azetidinone (**11**) is described.

In a series of studies on the development of new reactions using functional five-membered heterocycles,[1] we have prepared chiral 4(*R*)-methyl-5(*S*)-phenyl- and 4(*S*)-ethyl-1,3-oxazolidine-2-thiones,[2] 4(*R*),5(*S*)-MPOT and 4(*S*)-EOT, respectively. We now report a useful stereoselective synthesis of aldols[3] employing 4(*R*),5(*S*)-MPOT and 4(*S*)-EOT as chiral reagents and tin(II) trifluoromethanesulphonate and *N*-ethylpiperidine as enolating reagents.[4]

Thus, *N*-ethylpiperidine (1.6 mmol) was added to a suspension of tin(II) trifluoromethanesulphonate (1.5 mmol) in anhydrous CH_2Cl_2 (3.3 ml) at −50 °C under Ar. After addition of a solution of 3-acetyl-4(*R*),5(*S*)-MPOT (**1**) (1 mmol) in CH_2Cl_2 (1.2 ml), the mixture was stirred at *ca.* −50 to −40 °C for 3 h to complete the tin–enolate formation. Then, a solution of isobutyraldehyde (1.2 mmol) in CH_2Cl_2 (1.2 ml) was added at −78 °C and the mixture was stirred at the same temperature for 20 min. Usual work-up[4] of the reaction mixture gave a mixture of diastereoisomers (**2b**) and (**3b**), the ratio of which was readily checked by h.p.l.c. equipped with a u.v. detector.[2] Chromatographic separation of each diastereoisomer gave optically pure compounds (**2b**) {68% yield, colourless oil, $[\alpha]_D^{25}$ +36.60° (*c* 1.0, $CHCl_3$)} and (**3b**) {7.3% yield, colourless oil $[\alpha]_D^{25}$ +106.05° (*c* 0.48, $CHCl_3$)}. Similar chiral aldol reactions using compound (**1**), 3-acetyl-4(*S*)-EOT (**4**), 3-propanoyl-4(*R*),5(*S*)-MPOT (**7**), and 3-propanoyl-4(*S*)-EOT (**9**) gave also fairly high diastereoselectivity (see Scheme 1 and Table 1). Absolute configuration was confirmed by comparison of the physical data of β-hydroxycarboxylic acids (or their methyl esters) derived from the corresponding aldol products with those of the authentic samples[5] or by chemical correlation with a compound[6] whose stereochemistry had been confirmed by *X*-ray analysis.

All chiral recognition data listed in Table 1 can be rationalised by an assumed transition state (I). Comparison of this transition state with that in the Evans case (II)[7] shows a remarkable contrast.



Scheme 1. *Reagents and conditions:* i, $Sn(O_3SCF_3)_2$–*N*-ethylpiperidine, CH_2Cl_2, *ca.* −50 to −40 °C; ii, RCHO −78 °C.

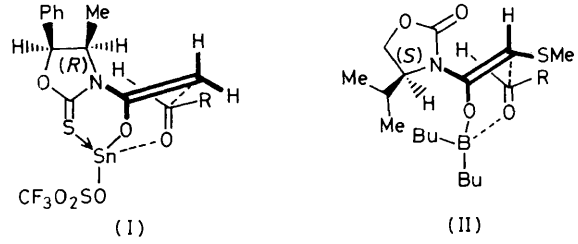
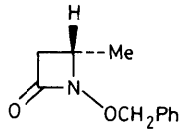


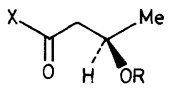
Table 1. Diastereoselective synthesis of aldols using chiral 3-acyl-1,3-thiazolidine-2-thiones (AOT).

AOT	Aldehyde	Diastereoisomer selectivity[a]	Isolated yield of major product/%
(**1**)	MeCHO	76.3 : 23.7 (**2a**) (**3a**)	62(**2a**)
(**1**)	Me_2CHCHO	89.0 : 11.0 (**2b**) (**3b**)	68(**2b**)
(**1**)	Me_2CHCH_2CHO	81.8 : 18.2 (**2c**) (**3c**)	64(**2c**)
(**4**)	Me_2CHCHO	91.4 : 8.6 (**6b**) (**5b**)	60(**6b**)
(**7**)	Me_2CHCHO	90.5 : 9.5[b] (**8b**)	71(**8b**)
(**7**)	PhCHO	83.7 : 16.3[b] (**8d**)	65(**8d**)
(**9**)	Me_2CHCHO	85.6 : 14.4[b] (**10b**)	74(**10b**)

[a] Determined by h.p.l.c. analysis (ref. 2). [b] Total number of other diastereoisomers.



(11)



(12) X = MPOT, R = $Si(Me_2)Bu^t$
(13) X = $NHOCH_2Ph$, R = $Si(Me_2)Bu^t$
(14) X = $NHOCH_2Ph$, R = H
(15) X = OEt, R = H

Finally, we applied this aldol reaction to the synthesis of a chiral azetidinone (**11**).[3] Alcohol (**2a**), after protection to give (**12**) (83.9% yield), was converted into amide (**13**) by aminolysis (56.8%) with *O*-benzylhydroxylamine in $CHCl_3$. Treatment of (**13**) with $Bu^n_4N^+F^-$ in tetrahydrofuran (THF) gave *N*-benzyloxy-3(*R*)-hydroxybutyramide (**14**) {m.p. 92—93 °C (AcOEt–hexane), $[\alpha]_D^{17}$ −28.0° (*c* 0.46, $CHCl_3$)} in 81.5% yield. Compound (**14**) was allowed to react with diethyl azodicarboxylate and triphenylphosphine[8] in THF to afford optically pure 1-benzyloxy-4(*S*)-methyl-2-azetidinone (**11**) {colourless oil, $[\alpha]_D^{17}$ −26.3° (*c* 1.0, $CHCl_3$)} in 84.1% yield.

The absolute configuration and optical purity of (**11**) were confirmed by chemical correlation with ethyl 3(*R*)-hydroxybutyrate (**15**).

Received, 10th June 1985; Com. 804

References

1 Y. Nagao, T. Ikeda, M. Yagi, E. Fujita, and M. Shiro, *J. Am. Chem. Soc.*, 1982, **104**, 2079; Y. Nagao, T. Miyasaka, K. Seno, E. Fujita, D. Shibata, and E. Doi, *J. Chem. Soc., Perkin Trans. 1*, 1984, 183; and references cited therein.
2 Y. Nagao, T. Kumagai, S. Yamada, E. Fujita, Y. Inoue, Y. Nagase, S. Aoyagi, and T. Abe, *J. Chem. Soc., Perkin Trans. 1*, in the press.
3 Orally reported at the '16th Congress of Heterocyclic Chemistry,' Osaka, Japan, October 1984.
4 N. Iwasawa and T. Mukaiyama, *Chem. Lett.*, 1983, 297.
5 D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.
6 Y. Nagao, Y. Hagiwara, T. Kumagai, S. Yamada, T. Inoue, M. Shiro, M. Ochiai, and E. Fujita, to be published.
7 D. A. Evans, J. M. Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre, and J. Bartroli, *Pure Appl. Chem.*, 1981, **53**, 1109.
8 *Cf.* P. G. Mattingly, J. F. Kerwin, Jr., and M. J. Miller, *J. Am. Chem. Soc.*, 1979, **101**, 3983 and ref. 2.